

A Multicomponent Intervention To Prevent Major Bleeding Complications in Older Patients Receiving Warfarin

A Randomized, Controlled Trial

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Background: Warfarin is effective in the treatment and prevention of many venous thromboembolic disorders, but it often leads to bleeding.

Objective: To develop a multicomponent program of management of warfarin therapy and to determine its effect on the frequency of warfarin-related major bleeding in older patients.

Design: Randomized, controlled trial.

Setting: University hospital in Cleveland, Ohio.

Patients: 325 patients 65 years of age or older who started warfarin therapy during hospitalization.

Interventions: Patients were stratified according to baseline risk for major bleeding and were randomly assigned to receive the intervention ($n = 163$) or usual care ($n = 162$) by their primary physicians for 6 months. The intervention consisted of patient education about warfarin, training to increase patient participation, self-monitoring of prothrombin time, and guideline-based management of warfarin dosing.

Measurements: Major bleeding, death, recurrent venous thromboembolism, and therapeutic control of anticoagulant therapy at 6 months.

Results: In an intention-to-treat analysis, major bleeding was more common at 6 months in the usual care group than in the intervention group (cumulative incidence, 12% vs. 5.6%; $P = 0.0498$, log-rank test). The most frequent site of major bleeding in both groups was the gastrointestinal tract. Death and recurrent venous thromboembolism occurred with similar frequency in both groups at 6 months. Throughout 6 months, the proportion of total treatment time during which the international normalized ratio was within the therapeutic range was higher in the intervention group than in the usual care group (56% vs. 32%; $P < 0.001$). After 6 months, major bleeding occurred with similar frequencies in the intervention and usual care groups.

Conclusions: A multicomponent comprehensive program of warfarin management reduced the frequency of major bleeding in older patients. Although the generalizability and cost-effectiveness of this program remain to be demonstrated, these findings support the premise that efforts to reduce the likelihood of major bleeding will lead to safe and effective use of warfarin therapy in older patients.

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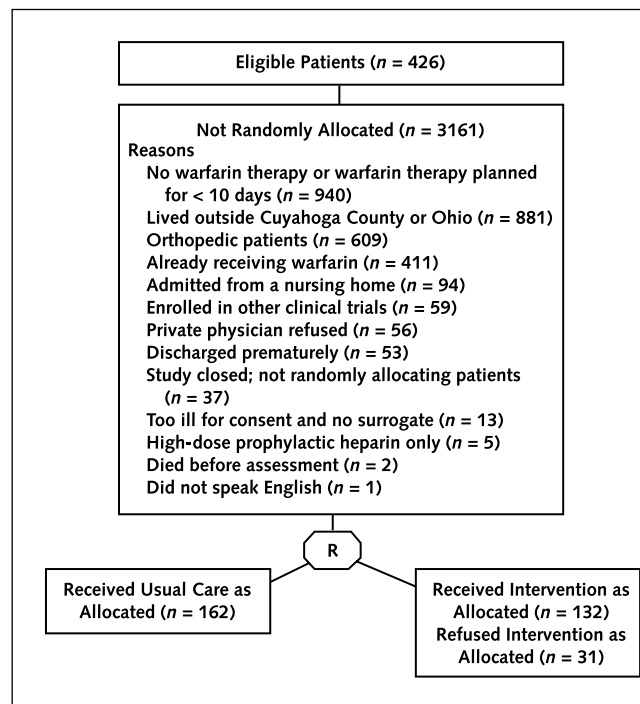
Bleeding is the major side effect of warfarin and is a major deterrent to its use, especially in older patients. Older people are widely thought to be at increased risk for warfarin-related bleeding (1–8), and they are less likely to be treated with warfarin, even when it has been proven efficacious, in part because of concern about risk for bleeding (9–13). Efforts that reduce the frequency of major warfarin-related bleeding not only will increase the net benefit of therapy but also will facilitate more appropriate and widespread use of warfarin therapy in older patients. Methods for identifying patients at highest risk for bleeding have recently advanced (5–7, 14–21), and experience with specialized programs that coordinate the management of anticoagulant therapy suggests that clinical outcomes may be improved (6, 14, 18, 22–27). However, there is little controlled or experimental evidence on how to optimize management of anticoagulant therapy in older patients and prevent bleeding.

We developed a multicomponent comprehensive program for management of warfarin therapy aimed at improving control of the anticoagulant effect and reducing events (such as use of an interacting medicine) that might precipitate bleeding. We hypothesized that this intervention would be acceptable to most elderly persons starting warfarin therapy and would reduce the frequency of warfarin-related major bleeding.

METHODS

Patients

Patients hospitalized at University Hospitals of Cleveland, a 900-bed teaching hospital, between September 1992 and October 1995 who were 65 years of age or older and were receiving 10 000 units or more of intravenous unfractionated heparin every 24 hours were screened daily. Of these patients, we identified 426 persons who were 65

Figure 1. Eligibility and random assignment of patients.

years of age or older, who resided in Cuyahoga County, Ohio, and for whom treatment with warfarin was planned for 10 or more days (Figure 1). Patients were excluded if they had been treated with warfarin at any time during the previous 6 months, were admitted from a nursing home, were enrolled in another clinical trial, were too ill to give consent and had no available surrogate, were discharged prematurely, or did not speak English; if their private physician refused to participate; or if no random allocation was taking place (for example, during vacations or holidays). Eligible patients who were enrolled did not differ significantly from those who were not enrolled with regard to age, ethnicity, sex, or indication for therapy.

Patients were stratified according to their baseline risk for major bleeding by using the Outpatient Bleeding Risk Index (20). This index includes four independent risk factors for major bleeding: age 65 years or older, history of gastrointestinal bleeding, history of stroke, and one or more of four specific comorbid conditions (recent myocardial infarction, hematocrit < 30%, creatinine concentration > 133 $\mu\text{mol/L}$ [1.5 mg/dL], or diabetes mellitus). Patients with one or two risk factors were classified as intermediate risk, and those with three or more risk factors

were classified as high risk; estimated frequencies of major bleeding in 6 months were 6% and 35%, respectively.

After stratification, patients were randomly assigned to receive usual care or intervention. Informed consent for observation and data collection was then sought from both groups, and informed consent to participate in the intervention was sought from the intervention group. This method, initially proposed by Zelen (28), allows the study to test the effectiveness of offering the intervention rather than simply the efficacy of the intervention in patients who consent to participation before random assignment. The sample size was calculated to provide 80% power and an α level of 0.05. The study protocol and informed consent procedures were approved by the hospital's institutional review board.

Intervention

The intervention had two main components. The first component consisted of a guideline-based consultation that assessed the patient's indications for therapy and potential risk factors for warfarin-related bleeding. We used this method previously to reduce the frequency of anticoagulant-related bleeding during hospitalization (27). Specific recommendations about modifiable risk factors, such as use of nonsteroidal anti-inflammatory drugs, were made and implemented. The study investigators directed warfarin dosing and international normalized ratio (INR) testing after hospital discharge. The second component included patient education, coaching, and self-monitoring of prothrombin time; this component was grounded in social learning theory (29–31) and experimental evidence (32, 33) showing that increasing participation of patients in their care can improve clinical outcomes but that increasing patient knowledge alone is insufficient (34, 35). Patient education consisted of one-on-one teaching by a lay educator using a specifically formatted workbook for older adults to teach them about warfarin, indications for its use, drug and food interactions, and the signs and symptoms of bleeding. The lay educator reviewed the workbook and was taught how to use the prothrombin time monitor by one of the authors but had no formal medical training. Coaching was aimed to increase patients' participation in their care and to improve information-seeking skills. Patients were trained and encouraged to communicate more effectively with physicians and other health personnel about a range of issues, such as health concerns, drug interactions,

or changes in lifestyle or diet. Finally, patients were taught to self-monitor the prothrombin time by using a home portable monitor (Coumatrak Protime Test System, Bio-track, Inc., Mountain View, California). The monitor uses a fingerstick to obtain a blood sample and has well-established accuracy (36–38).

Patients were initially assessed, educated, and taught to use the portable monitor while hospitalized; training lasted 30 minutes to 1 hour. They were seen daily while hospitalized, warfarin therapy was adjusted as needed, and any concerns or questions about anticoagulant therapy were addressed. Within 3 days of discharge from the hospital, the lay educator or study investigator made a home visit to assess patients' use of the portable monitor and to check the prothrombin time. In general, patients were instructed to check their prothrombin time three times during the first week after hospital discharge, weekly for the remainder of the first month, and monthly thereafter depending on their results. Patients phoned in their results to the coach, who reviewed the results with one of the investigators and provided same-day follow-up, including recommendations for dose and subsequent INR testing. Patients were instructed to call whenever they had questions or concerns about their warfarin management or possible side effects, if they were hospitalized for any reason, or if they began receiving new medications. After the 6-month intervention period, management and dosing of warfarin therapy reverted back to patients' personal physicians.

Patients assigned to usual care received medical care, including management, dosing, and medical information, according to the discretion and practices of their personal physician.

Data Collection

Trained abstractors who were not involved with the intervention component of the study collected data from the medical chart at the start of anticoagulant therapy; at each subsequent hospitalization; and by blinded interview at enrollment and 1, 3, and 6 months after enrollment and every 6 months thereafter. Data elements included demographic characteristics, clinical history including comorbid diagnoses, indications for therapy, potential risk factors for bleeding, functional status, and new illnesses or comorbid conditions that developed after enrollment. Surveillance for bleeding and thromboembolism was conducted identically in the intervention and control groups and consisted

of 12 items inquiring about bleeding and thromboembolism at each follow-up interview. Whenever an event was reported, the clinical characteristics of the bleeding or thromboembolic episode were determined by review of the relevant medical record and abstracted without identifying patient information onto a standard form. All dates of death were confirmed by death certificates, and all causes of death were confirmed by review of death certificates and medical records. Follow-up was complete for all patients.

End Points

The primary end point was the first major bleeding event during the 6-month intervention period. Using explicit criteria in the Bleeding Severity Index (39) for the amount, rate, and consequences of bleeding, we defined major bleeding as overt bleeding that led to the loss of at least 2.0 units of blood in 7 days or less or was otherwise life-threatening (for example, intracranial bleeding). Bleeding was classified without information about possible risk factors or randomization status. Two author-reviewers who were blinded to group assignment adjudicated bleeding events; their agreement was high (κ statistic, 0.97).

Secondary outcomes were death and recurrent venous thromboembolism at 6 months; major bleeding after 6 months; and control of anticoagulant therapy during the first 6 months of therapy, as measured by the INR. The therapeutic range of the INR was defined as 2.5 to 3.5 for persons with mechanical heart valves and 2.0 to 3.0 for persons with all other indications (40). Therapeutic quality control was assessed by using the "patient-time" approach, described by Rosendaal and colleagues (41), for three time periods after discharge from the hospital: 0 to 1 month, 1 to 3 months, and 3 to 6 months of therapy. This approach estimates the amount of time a patient is in the therapeutic range based on the actual INRs measured, assuming a linear relationship between consecutive INRs. Patients with only one INR measurement during the time period and those not discharged with continued warfarin therapy were excluded from the analyses.

Statistical Analysis

Statistical analyses of all outcomes were performed on an intention-to-treat basis. The rate of major bleeding during the 6-month intervention was determined. The rates of major bleeding during hospitalization and at 1 month and

Table 1. Patient Characteristics

Characteristic	Intervention Group (n = 163)	Usual Care Group (n = 162)	P Value
Age, n (%)			
65–70 years	50 (30)	51 (32)	>0.2
71–75 years	47 (29)	46 (29)	
76–80 years	32 (20)	34 (20)	
81–85 years	19 (12)	19 (12)	
≥86 years	15 (9)	12 (7)	
Mean age ± SD, y	74.9 ± 6.9	74.5 ± 6.6	>0.2
Female, n (%)	89 (55)	95 (59)	>0.2
White, n (%)	113 (69)	106 (65)	>0.2
Primary indication for therapy, n (%)			
Venous thromboembolism	60 (37)	64 (40)	>0.2
Atrial fibrillation	27 (17)	27 (17)	>0.2
Cerebrovascular disease	25 (15)	24 (15)	>0.2
Heart valve prosthesis	23 (14)	13 (8)	0.1
Other*	19 (12)	22 (14)	>0.2
Peripheral vascular disease	6 (4)	8 (5)	>0.2
Myocardial infarction	3 (2)	4 (2)	>0.2
Comorbid conditions at the start of therapy, n (%)			
History of hypertension	88 (54)	85 (53)	>0.2
History of gastrointestinal bleeding	9 (5)	9 (5)	>0.2
Active cancer	24 (15)	22 (14)	>0.2
Renal disease†	16 (10)	20 (12)	>0.2
Risk for bleeding, n (%)			>0.2
Middle	139 (85)	138 (85)	
High	24 (15)	24 (15)	
Mean Charlson comorbidity index score	2.1 ± 1.9	2.2 ± 1.9	>0.2
Mean number of school years completed‡	12.1 ± 4.4	12.1 ± 4.1	>0.2
Living arrangement, n (%)			
Lives with spouse§	71 (49)	71 (48)	>0.2
Lives alone§	45 (31)	52 (35)	
Lives with other§	30 (20)	26 (17)	
Lives in private residence with no outside assistance	118 (80)	125 (83)	>0.2

* Other venous clots (n = 12), congestive heart failure (n = 8), other arterial clots (n = 7), left ventricular clots (n = 6), systemic emboli (n = 4), and left ventricular aneurysm or aneurysctomy (n = 4).

† Serum creatinine concentration ≥ 133 μmol/L.

‡ Data were available for 296 patients (91%).

§ Data were available for 295 patients (91%).

|| Data were available for 298 patients (92%). "Outside assistance" referred to assistance from a home health care aide, homemaker, or visiting nurse.

6 months after discharge were also ascertained. Control of therapy and other secondary outcomes were evaluated.

Differences between groups were evaluated by using the chi-square statistic for categorical variables, the Wilcoxon rank-sum statistic for continuous variables, and the log-rank test for survival curves. All tests of significance were two-tailed. Cumulative incidences of major bleeding were determined by using the Kaplan–Meier technique. Patients were censored at the first major bleeding event, death, or cessation of anticoagulant therapy, whichever came first. All analyses were performed by using SAS software (SAS Institute, Inc., Cary, North Carolina).

Role of the Funding Source

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RESULTS

The mean age of the patients was 75 years (range, 65 to 94 years). Fifty-seven percent of patients were women, and 67% were white. The primary indication for warfarin therapy was venous thromboembolism in 38% of patients, atrial fibrillation in 17%, cerebrovascular disease in 15%, heart prosthesis in 11%, and other indications in 19%. The baseline risk for bleeding was classified as intermediate in 85% of patients and high in 15%. At enrollment, the intervention group and the usual care group did not differ in clinical or sociodemographic variables (Table 1).

Among the 163 patients randomly assigned to the intervention group, 132 (81%) participated in the intervention. Of the 163 patients, 46 patients (28%) monitored their prothrombin time themselves; 50 (31%) had a spouse, other relative, or visiting nurse help with their prothrombin time monitoring; and 36 (22%) were monitored conventionally without self-monitoring (20 had physical limitations, such as severe arthritis or decreased vision; 12 felt more comfortable with venipuncture; 3 stopped warfarin therapy during the index hospitalization; and 1 was discharged to a nursing home that precluded use of the portable monitor). Thirty-one patients (19%) declined to participate in the intervention; their anticoagulant therapy was managed by their personal physician.

The cumulative incidences of major bleeding at 1, 3, and 6 months were 4.6%, 4.6%, and 5.6%, respectively, in the intervention group and 7%, 12%, and 12%, in the usual care group ($P = 0.0498$, log-rank test) (Figure 2). The most common site of bleeding during the 6 months was the gastrointestinal tract in both groups (Table 2). Major bleeding was fatal in one patient in the intervention

group and three patients in the usual care group. Excessive anticoagulation and a recent history of an invasive procedure or surgery at the time of major bleeding were more common among patients in the usual care group than among those in the intervention group (Table 2). Of the eight major bleeding events that occurred in the intervention group, six occurred in patients who had declined the intervention, including the one patient with fatal gastrointestinal bleeding and two patients with intracranial bleeding.

Almost half (12 of 25) of the major bleeding events occurred during the index hospitalization; of these, 3 occurred in the intervention group and 9 occurred in the usual care group ($P = 0.08$). The respective cumulative incidences of major bleeding were 2.7% and 2.2% at 1 month after discharge and 3.7% and 6.5% at 6 months after discharge among patients who survived to discharge ($P > 0.2$ by log-rank technique). After 6 months, major bleeding occurred in 2 patients in the intervention group and 3 patients in the usual care group ($P > 0.2$).

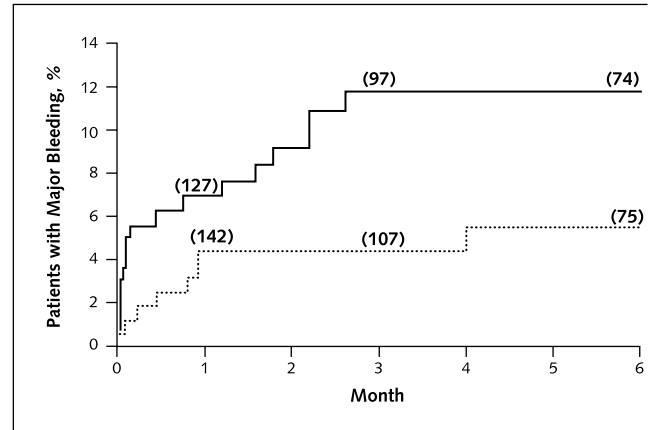
A total of 4091 INR measurements were taken during 26 065 patient-days of follow-up; the median number of determinations per patient was 17 (range, 2 to 39) in the intervention group and 10.5 (range, 2 to 44) in the usual care group. Patients in the intervention group were within the therapeutic range at each of the three time periods significantly more often than were patients who received usual care (proportion of total treatment time with INR in the therapeutic range, 56% vs. 32%; $P < 0.001$) (Table 3).

At 6 months, 21 patients (13%) in the intervention group and 26 patients (16%) in the usual care group ($P > 0.2$) had died. The difference in the death rates between the groups was 0.011 death per patient-month (95% CI, -0.01 to 0.03). Recurrent venous thromboembolism at 6 months occurred in 14 patients (8.6%) in the intervention group and 21 patients (13%) in the usual care group ($P = 0.2$). The difference in recurrence rates between the two groups was 0.013 recurrence per patient-month (CI, -0.005 to 0.031).

DISCUSSION

We found that a comprehensive program of anticoagulant management reduced the frequency of major bleeding in older patients randomly assigned to be offered the intervention at the start of long-term anticoagulant therapy in the hospital. The intervention was acceptable to most older patients to whom it was offered, did not require

Figure 2. Cumulative incidence of major bleeding at 6 months according to intention-to-treat analysis in patients who received usual care ($n = 162$) (solid line) and those who received the study intervention ($n = 163$) (dotted line).



Numbers in parentheses are the number of patients without bleeding who were still treated with warfarin at that time point. $P = 0.05$, log-rank test.

extensive training, and could be implemented in a manner similar to the use of a home glucometer. The greatest difference between the intervention and usual care groups in the frequency of major bleeding occurred during the first week (when anticoagulant therapy was started in the hospital) and after the first month of therapy (when outpatient therapy was presumably stabilized). The groups differed little during the second through fourth weeks of therapy, when patients were generally discharged and warfarin was first monitored in the outpatient setting.

The improvements in patient outcomes were accompanied by substantial and consistent differences between the intervention and usual care groups in control of the anticoagulant effect. For patients in the intervention group, the INR was in the therapeutic range more than half the time—nearly twice as much of the time as that in the usual care group. In the usual care group, the INR was supratherapeutic more than one third of the time during the first month of outpatient therapy and was subtherapeutic most of the time thereafter.

Various approaches to the comprehensive management of long-term anticoagulant therapy have been described (6, 14, 18, 22–26), but their effects on the process and outcomes of care have not been evaluated. Patient education and self-management of anticoagulant therapy can improve anticoagulant control in carefully selected

patients (42), but the effects of this approach on patient outcomes is unknown. Other advances that may improve management of anticoagulant therapy include use of lower-intensity therapy for venous thrombosis (43) and in the setting of prosthetic valves (44), identification of risk factors for bleeding and risk stratification of patients (2, 6, 7,

14, 15, 18, 20, 21), use of INR as a measure of anticoagulant effect (45, 46), and portable prothrombin time monitors (42, 47-50). We previously evaluated the efficacy of consultation on the frequency of in-hospital bleeding in patients treated with heparin or warfarin and demonstrated a reduction in this event from 31% to 13% (27). The

Table 2. Characteristics of Patients with Major Bleeding at 6 Months

Patients with Major Bleeding	Day*	Anticoagulant Therapy	International Normalized Ratio	Activated Partial Thromboplastin Time	Site of Bleeding	Potential Risk Factors
Intervention group (n = 8)	0	Intravenous unfractionated heparin and warfarin at index hospitalization	1.3	>200 s	Gastrointestinal	Simultaneously taking ibuprofen; declined intervention
	3	Intravenous unfractionated heparin and warfarin at index hospitalization	1.8	2.0 times control value	Genitourinary	Known metastatic prostate cancer
	7	Outpatient warfarin	1.4		Intracranial	Declined intervention
	14	Intravenous unfractionated heparin and warfarin at index hospitalization	2.0	1.5 times control value	Gastrointestinal†	Newly diagnosed lung cancer; declined intervention
	25	Outpatient warfarin	16.3		Gastrointestinal	Declined intervention
	28	Outpatient warfarin	3.4		Gastrointestinal	Declined intervention
	28	Outpatient warfarin	7.6		Intracranial	Recently started taking sotalol; declined intervention
	122	Outpatient warfarin	2.1		Intracranial†	
Usual care group (n = 17)	0	Intravenous unfractionated heparin and warfarin at index hospitalization	3.7	>200 s	Soft tissue	Recent procedure
	1	Intravenous unfractionated heparin and warfarin at index hospitalization	18.0	>200 s	Soft tissue	Recent procedure
	1	Intravenous unfractionated heparin and warfarin at index hospitalization	6.2	>100 s	Hemothorax	Recent procedure
	1	Intravenous unfractionated heparin and warfarin at index hospitalization	1.1	2 times control value	Soft tissue	Recent surgery
	1	Intravenous unfractionated heparin and warfarin at index hospitalization		1.5 times control value	Soft tissue	Recent procedure
	2	Intravenous unfractionated heparin and warfarin at index hospitalization	2.0	2 times control value	Gastrointestinal	
	3	Warfarin at index hospitalization	8.9		Gastrointestinal	Simultaneously taking aspirin
	3	Intravenous unfractionated heparin and warfarin at index hospitalization	1.3	1.5 times control value	Soft tissue	
	5	Intravenous unfractionated heparin only at index hospitalization		1.8 times control value	Hemothorax‡	Recent procedure
	14	Outpatient warfarin	2.4		Gastrointestinal†	
	23	Outpatient warfarin	7.7		Pericardial	Simultaneously taking aspirin; recently started taking ciprofloxacin
	38	Outpatient warfarin	3.2		Gastrointestinal	Newly diagnosed colon cancer
	49	Outpatient warfarin	24.3		Gastrointestinal	
	56	Outpatient warfarin	214		Gastrointestinal	
	67	Outpatient warfarin	7.1		Gastrointestinal	
	67	Outpatient warfarin	4.3		Gastrointestinal†	Simultaneously taking aspirin
80	Outpatient warfarin	3.4		Gastrointestinal		

* Time from randomization to major bleeding event.

† Patient actively participated in the intervention.

‡ Fatal bleeding.

Table 3. Therapeutic Control with Warfarin in the First 6 Months of Outpatient Therapy*

INR	Proportion of Time Spent in INR Ranges†					
	0–1 Month (n = 261)		1–3 Months (n = 230)		3–6 Months (n = 165)	
	Intervention Group	Usual Care Group	Intervention Group	Usual Care Group	Intervention Group	Usual Care Group
	← % →					
Subtherapeutic	32.2	33.9	29.9	52.1‡	30.9	50.4‡
Therapeutic§	48.6‡	31.4	58.9‡	29.5	58.5‡	34.2
Supratherapeutic	19.2	34.7‡	11.3	18.4‡	10.6	15.41‡

* INR = international normalized ratio.

† Percentage of the total observation time for each treatment group using an intention-to-treat analysis. The number of patients who had sufficient data available for calculations is given in parentheses.

‡ $P < 0.001$.

§ Defined as an INR of 2.5 to 3.5 for persons with mechanical heart valves and 2.0 to 3.0 for persons with all other indications, as recommended by the Fourth American College of Chest Physicians Consensus Conference on Antithrombotic Therapy (40).

current study was designed to incorporate these recent advances in a comprehensive, multicomponent intervention and to evaluate this intervention in a randomized, controlled trial.

Despite the low rates of warfarin-related bleeding achieved in several randomized trials of the efficacy of warfarin (51–55), higher rates of major bleeding have been reported in many observational studies of warfarin used in practice outside the clinical trial setting (6, 7, 14, 15, 18, 21, 56, 57). Thus, it has been unclear whether lower rates of bleeding could be achieved in practice. In this study, the sample was assembled with few exclusion criteria and consisted of a heterogeneous group of older persons; the bleeding rates in the usual care group were similar to those in previous observational studies. The comprehensive intervention achieved a frequency of major bleeding in participating patients that was similar to the lower rates achieved in previous randomized trials of the efficacy of warfarin.

Several methodologic considerations support the validity of our major findings. The experimental study design, random assignment of patient, and intention-to-treat analysis make it unlikely that our findings are attributable to unrecognized confounding or selection bias. Although data collection could not be blinded to group assignment, measurement bias was minimized by systematic surveillance of the intervention and control groups, use of an explicit and highly reliable method for classifying the major outcomes, and blinding to group assignment of outcome classification. The conclusion that the intervention was beneficial is further supported by the consistency of the intervention's apparent effects on bleeding, recurrent thromboembolism, and INR control.

The study was not designed to determine the relative

importance of the components of the intervention. Thus, we cannot determine how much of the improved INR control and lower bleeding rate are attributable to patient education, patient participation, or expert guidance of warfarin monitoring and dosing. Our study also did not determine why some patients declined to participate in the intervention program; these patients, one quarter of whom developed major anticoagulant-related bleeding, may benefit greatly from efforts to understand and reduce their risks for bleeding. A formal cost analysis is beyond the scope of this study. We estimate the cost of self-monitoring for 6 months to be \$1385 (\$1295 for a monitor plus \$90 for 6 months of supplies). Finally, we studied hospitalized older patients starting long-term anticoagulant therapy. The benefit of the intervention has not been demonstrated in other patients, such as outpatients starting anticoagulant therapy, and the intervention would probably have less incremental benefit in settings in which usual care achieves the high rates of INR control achieved by the intervention.

A comprehensive program of anticoagulant management should be considered in typical clinical settings; the rate of major bleeding may be cut by half or more over 6 months, and the rate of death or recurrent thromboembolism may be reduced by one quarter. Extending such an intervention to other settings may promote appropriately more widespread use of warfarin to prevent stroke and other serious thromboembolism in older patients who may now go untreated (9–12, 58–60).

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